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Fatores relacionados à inflamação na hipertrofia cardíaca induzida pelo hormônio tiroideano. Contribuição do sistema renina-angiotensina

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RESUMO

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Recentes trabalhos evidenciam a participação de mecanismos de resposta inflamatória no desenvolvimento da hipertrofia cardíaca e outras consequências no sistema cardiovascular. Resultados prévios ainda não publicados demonstraram um aumento de genes relacionados ao processo inflamatório em corações de ratos tratados com hormônios tiroideanos (HT). Além disso, sabe-se o Sistema Renina-Angiotensina (SRA) induz uma resposta inflamatória no sistema cardiovascular, bem como participa do desenvolvimento da hipertrofia cardíaca induzida pelos elevados níveis de HT. Baseado nestas evidências, o presente estudo avaliou aspectos relacionados ao contexto inflamatório na hipertrofia cardíaca induzida pelos HT e o possível envolvimento do SRA nesse processo, utilizando análises in vivo e in vitro. Os dados obtidos mostraram algumas alterações nos níveis de citocinas circulantes e cardíacas de animais tratados com HT. A expressão de calgranulina A (ou também conhecida como S100A8) e do fator de diferenciação mielóide 88 (MyD88) apresentaram-se bem elevados no tecido cardíaco de animais submetidos ao hipertiroidismo, bem como em cardiomiócitos em cultura estimulados com HT. A participação destas moléculas na hipertrofia dos cardiomiócitos em resposta aos HT foi também evidenciada. Ainda, S100A8 e MyD88 atuam como cruciais mediadores da ativação do fator nuclear kappa B (NF-κB), o qual também apresenta um papel fundamental no crescimento hipertrófico de cardiomiócitos tratados com HT. Por fim, a ação dos HT modulando a expressão de S100A8 e NF-κB está sob influência do SRA ou, mais especificamente, da participação do receptor de angiotensina tipo 1 (AT1) mediando os efeitos provocados pelos HT. Estes dados contribuem com o entendimento das bases moleculares da ação dos HT no tecido cardíaco, bem como da relação deste com o SRA, considerando a importante influência da interação destes sistemas endócrinos no desenvolvimento de uma série de alterações na fisiopatologia cardiovascular.

Palavras-chave: Hormônio tiroideano. Hipertrofia cardíaca. Cardiomiócito. Sistema renina-angiotensina. Inflamação. NF-κB.

ABSTRACT

TAKANO, A. P. C. **Inflammation-related aspects in cardiac hypertrophy induced by thyroid hormone. Contribution of the renin-angiotensin system.** 2016. 104 p. Ph. D. thesis (Morphological Sciences) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2016.

Recent studies have evidenced the involvement of inflammatory related mechanisms to the development of cardiac hypertrophy and other consequences on cardiovascular system. Previous unpublished results demonstrated increased pro-inflammatory genes in heart of rats treated with thyroid hormone (TH). In addition, it is well known that the renin-angiotensin system (RAS) induce inflammatory response on cardiovascular system and mediate the cardiac hypertrophy induced by high levels of TH. Based on those evidences, the present study evaluated some aspects related to the inflammatory context in the cardiac hypertrophy induced by TH, and the possible involvement of RAS in this process, by using in vivo and in vitro analysis. The data showed some alterations in circulating and cardiac cytokines from TH-treated animals. The expression of calgranulin A (or also known as S100A8) and the myeloid differentiation factor-88 (MyD88) were increased in cardiac tissue of hyperthyroid animals and in cultured cardiomyocytes under T3 stimulation. The contribution of those molecules in the cardiomycyte hypertrophy in response to TH was also demonstrated. Furthermore, S100A8 and MyD88 were crucial mediators of nuclear factor kappa B (NF-κB) activation, which is also fundamental to the hypertrophic growth of TH-treated cardiomyocytes. Finally, the TH action modulating the expression of S100A8 and NF-κB was influenced by RAS, or specifically, by the contribution of angiotensin type 1 receptor (AT1) mediating the TH effects. These data contribute to the knowledge of molecular basis of TH action on cardiac tissue, as well as the crosstalk between TH and RAS, considering the important influence of both endocrine systems to the development of many alterations in the cardiovascular physiopathology.

Keywords: Thyroid hormone. Cardiac hypertrophy. Cardiomyocyte. Renin-angiotensin system. Inflammation. NF-κB.

1 INTRODUÇÃO

Recentes estudos vêm evidenciando que o desenvolvimento e a progressão de grande parte das doenças cardiovasculares é acompanhada pelo acionamento de mecanismos relacionados à resposta inflamatória (BAUMGARTEN et al., 2006; LIN; KNOWLTON, 2014; MANN, 2011; ZHANG et al., 2015). Considerando isso, dados ainda não publicados do nosso grupo indicaram que alguns genes relacionados ao processo inflamatório encontram-se ativados em corações de ratos tratados com hormônios tiroideanos (HT). Os HT agem nos mais diferentes tipos celulares promovendo, de modo geral, ações que levam ao aumento do metabolismo basal. No sistema cardiovascular, elevados níveis de HT exercem profundos efeitos morfológicos e funcionais, os quais culminam com a instalação de um processo de hipertrofia cardíaca, que dependendo de seu grau, pode culminar para um prejuízo funcional e uma situação de insuficiência cardíaca.

A hipertrofia cardíaca, assim como outros efeitos cardiovasculares resultantes da ação dos HT é mediada em parte por outros sistemas endócrinos como o Sistema Nervoso Simpático (através da ação beta-adrenérgica) e o Sistema Renina-Angiotensina (SRA) (BARRETO-CHAVES et al., 2010; HU et al., 2003). Embora hoje se saiba que o SRA compreende vários novos peptídeos e enzimas, as ações mais descritas até o momento ocorrem principalmente pela Angiotensina II, via receptor do tipo 1 (AT1), sendo esta capaz de gerar em vários tecidos, incluindo o tecido cardíaco, não só efeitos pró-hipertróficos, mas também pró-inflamatórios. Esta resposta se deve, pelo menos em parte, a mecanismos intracelulares que culminam com a ativação de fatores de transcrição como o fator nuclear kappa B (NF-κB) (BHATT; LOKHANDWALA; BANDAY, 2014; BRASIER et al., 2000; HASHIKATA et al., 2015; HE et al., 2015; SUZUKI et al., 2003).

A ativação do NF-κB apresenta papel crítico na regulação da expressão de grupos de genes envolvidos na resposta inflamatória, na sobrevivência, bem como no crescimento de diferentes tipos celulares, incluindo cardiomiócitos (GORDON; SHAW; KIRSHENBAUM, 2011). Além disso, vários trabalhos já demonstraram o envolvimento do NF-κB na instalação e no desenvolvimento da hipertrofia cardíaca resultante de distintos modelos experimentais in vivo e in vitro (GUPTA et al., 2002; JAVAN et al., 2015; LI et al., 2004; PURCELL et al., 2001; RAJAPUROHITAM et al., 2012; XU et al., 2015; ZELARAYAN et al., 2009).

Baseado nestas evidências, o presente estudo avalia o possível envolvimento deste fator de transcrição relacionado ao contexto inflamatório com a hipertrofia cardíaca (in vivo) ou cardiomiocítica (in vitro) deflagrada por elevados níveis de HT. Basicamente, o foco do estudo foi avaliar o efeito dos HT na sinalização envolvendo a calgranulina A (ou também conhecida como S100A8), o receptor *Toll like* tipo 4 (TLR4) e o fator de diferenciação mielóide 88 (MyD88), a qual está diretamente relacionada à ativação do fator NF-κB. O papel desta sinalização na instalação da hipertrofia, bem como o possível envolvimento do SRA, via receptor AT1, neste processo, foi ainda objeto deste estudo.

Uma descrição mais detalhada sobre a hipertrofia cardíaca que se observa em resposta a elevados níveis de HT, sua relação com a ativação do SRA bem como a contribuição da sinalização relacionada ao NF-κB neste processo encontram-se a seguir.

7 CONCLUSÃO

Com base nos resultados obtidos e descritos neste estudo, podemos resumidamente concluir que:

Os HT, através de S100A8 e S100A9 (ou calgranulinas A e B), estimulam a via de sinalização TLR4/ MyD88/ NF-κB, a qual apresenta papel crucial na hipertrofia dos cardiomiócitos, tendo o SRA, via AT1, função mediadora dos efeitos dos HT na ativação desse eixo.

Esses dados em conjunto indicam um novo mecanismo associado a vias ligadas à inflamação através das quais os HT atuam para induzir a hipertrofia dos cardiomiócitos, com participação do receptor AT1.

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